REMARKS

Status of the Claims

Claims 1-23 remain in the case. Claims 1-8 are amended herein. Support for the amendments can be found in previous claims 1-8.

Claims 9-23 are new. Support for new claims 9-11 and 19-21, reciting specific devices (i.e., a catheter and a stent) may be found at page 6, line 16 in Example 1, page 15, line 24 in Example 2, and page 24, lines 26-27 of the application as filed. Support for new claims 12-13 and 22-23 maybe be found in Examples 1 and 2, page 24, lines 26-29 of the application as filed. Support for new claims 14-18 may be found at original claims 1-8. No new matter has been added.

Rejections Under 35 USC §101

Applicants submit that this rejection has been overcome by the appropriate amendments to the claims. Specifically, claims 1-8 were rejected as reciting a use without reciting a step. As amended, the present claims recite a method having a least one positive step in accordance with 35 USC §101. Therefore, Applicants respectfully request this rejection be withdrawn.

Rejections Under 35 USC §112, Second Paragraph

Applicants submit that this rejection has been overcome by the appropriate amendments to the claims. Specifically, claims 1-8 were rejected as reciting a use without reciting a step. As amended, the present claims recite a method having a least one positive step in accordance with 35 USC §112, second paragraph.

Claims 1-8 were also rejected because it was not clear whether they were directed to a method of administering a medication having 17-β estradiol or whether the claims were directed to making a medication comprising 17-β estradiol. However, as amended, the present claims clearly recite a method of administering 17-β estradiol or a derivative thereof.

Claim 5 was rejected for lacking antecedent basis. As amended, this rejection has been overcome.

In view of the above remarks, it is respectfully requested that the rejection under 35 USC §112, second paragraph, be withdrawn.

Rejections Under 35 USC §102

Claims 1 and 8 have been rejected as being anticipated by U.S. Patent No. 5,866,561 to Ungs (Ungs) under 35 USC §102. This rejection is traversed because 1) Ungs does not disclose administration of estradiol at the injured site; and 2) Ungs does not disclose the administration of estradiol for improving reendothelization and vascular function.

As noted by the Examiner, Ungs teaches applying estrogen to the blood vessel walls at a treatment site proximal to or upstream of stenosis as an alternative means to increase perfusion when PTCA is impracticable (see col. 1, lines 52-64 of Ungs). Therefore, the method taught in Ungs is useful when PTCA may not be performed because the stenosed region is not accessible (see col. 2, lines 9-15 of Ungs). Accordingly, Ungs teaches applying estradiol to an uninjured site on a blood vessel to promote generation of other vessels or to increase permeability so that more blood can reach ischemic tissue. See, for instance, the abstract, of the field of the invention at col. 1, line 5 and col. 2, lines 6-7 of Ungs.

Further, Ungs is silent regarding using estradiol to increase reendothelization and vascular function at an injured site. Although Ungs appears to recognize that it is useful to promote endothelial cell growth after injury, vascular endothelial growth factor (VEGF) is the only agent discussed as being suitable for such a purpose (see col. 1, lines 30-34 of Ungs). The use of estradiol to promote and increase reendothelization and vascular function is not discussed. Further still, as noted above, Ungs is not directed towards the repair of injured blood vessels. Rather, Ungs is directed to a method of promoting the generation of new vessels and to increase blood permeability. In short, Ungs does not provide any working examples suggesting the estradiol is useful for promoting angiogenesis, let alone useful in repairing blood vessels.

Rejections Under 35 USC §103(a)

Claims 2-4 have been rejected as being obvious over Ungs in view of U.S. Patent No. 5,512,557 to Collins (Collins).

Claims 5-7 have been rejected as being obvious over Ungs in view of U.S. Patent No. 4,727,065 to Pitha (Pitha).

As discussed above, Ungs teaches the use of estradiol at a site proximal to or upstream to a stenosed region of a blood vessel to promote angiogenesis. Ungs is silent

regarding the effect of estradiol on reendothelization and vascular endothelial function. Further, Ungs provides no experimental data for either use.

Further still, even if Ungs had shown estradiol to be proangiogenic, Ungs still does not make using estradiol to improve reendothelization and vascular function obvious. For instance, many agents known to be proangiogenic are not used to promote vessel repair. Specifically, vascular endothelial growth factor (VEGF) is a known angiogenic agent that has attracted attention as a potentially good agent for promoting endothelial regeneration and endothelial function in injured vessels. However, its utility for this purpose was shown to be limited (see Exhibit A attached). Although VEGF promotes endothelial regeneration, it also increases inflammation and microangiogenesis-derived hemorrhage. Combined, these events can destabilize vulnerable plaques and provoke atherosclerosis and thrombosis (i.e., clogging, narrowing, and hardening of the body's large arteries and medium-sized blood vessels). Therefore, Applicants submit that at the time of filing, one of ordinary skill in the art could not predict the utility of estradiol to repaired injured vessels even if estradiol was a known angiogenic agent.

Collins teaches treating coronary heart disease in women with systemic administration of estradiol (see col. 1, lines 1-21 of Collins). However, Collins does not teach or suggest in situ administration of estradiol. While Collins does discuss various formulations of estradiol for oral, parenteral, anal or transdermal administration (see col. 2, lines 1-15 of Collins), the dosages disclosed in the working examples are sublingual (see col. 3, line 31). Therefore Collins' conclusions appear to be based solely on measures of heart rate and blood pressure. Further, Collins is silent regarding the effect of estradiol on reendothelization or vascular endothelial function.

Pitha teaches that the solubility of 17-β estradiol is increased in various cyclodextrins. Pitha is silent regarding any role of estradiol in reendothelization or vascular endothelial function.

As further support of the nonobviousness of the present claims, a Declaration by Dr. Richard Sean Stack M.D., originally submitted to the Japanese Patent Office during prosecution of the Japanese counterpart of this application, is enclosed as Exhibit B, along with Dr. Stack's curriculum vitae. In the Declaration, Dr. Stack explains the differences between restenosis, reendothelization and vascular endothelial function.

Therefore, in light of the above remarks, Applicants respectfully submit that neither Ungs, Collins or Pitha, alone or in combination, disclose or suggest that estradiol can be administered at an injured site of a vessel to improve reendothelization or vascular endothelial function. Applicants respectfully request this rejection be withdrawn.

Conclusion

It is submitted that the application is in condition for allowance. Favorable reconsideration is respectfully requested.

Other than the extension fee, additional fees are not believed to be needed for this amendment. However, if additional fees are needed, please charge them to Deposit Account No. 17-0055.

Respectfully submitted,

Baskaran Chandrasekar, et al.

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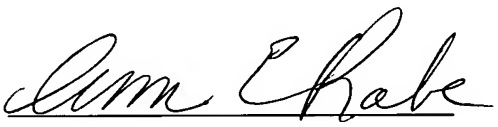
By: 

Ann E. Rabe
Registration No. 56,697
Quarles and Brady LLP
411 East Wisconsin Ave.
Milwaukee, WI 53202
(414) 277-5709